REMARKS

Applicants thank the Examiner for review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 1-5 are presented for examination.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Actions. The PTO states that the specification discloses that the PRO1557 polynucleotide is more highly expressed in esophageal and kidney tumor tissue compared to normal esophageal and kidney tissue, respectively. However, the PTO rejects Applicants' asserted utility, explaining that "even if the encoding polynucleotide has utility, on [*sic*] cannot on that basis alone support a utility for the encoded protein or antibody because the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable." *Final Office Action* at page 2.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that, for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1557 polypeptide is more highly expressed in esophageal and kidney tumor tissue compared to normal esophageal and kidney tissue, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given Applicants' evidence that the mRNA for the PRO1557 polypeptide is more highly expressed in esophageal and kidney tumor tissue compared to normal esophageal and kidney tissue, respectively, it is more likely than not that the PRO1557 polypeptide is also differentially expressed in esophageal tumor tissue and kidney tumor tissue compared to their normal tissue counterparts, making the claimed antibodies that specifically bind to the PRO1557 polypeptide useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating for example that there is insufficient guidance in the specification as to sample size, expression level range, and repeatability of the results, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, citing Hu *et al.* (J. Proteome Res., (2003) 2(4):405-12) for support;

2. The PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) and Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302), as supporting the assertion that "the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable." *Final Office Action* at page 2. Therefore, further research needs to be done to determine if the increase or decrease in PRO1557 cDNA expression supports a role for the peptide in cancerous tissue.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The Data Reporting Differential Expression of PRO1557 mRNA are Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants turn to the PTO's argument that the evidence of differential expression of the gene encoding the PRO1557 polypeptide in normal esophageal tissue and normal kidney tissue compared to esophageal tumor tissue and kidney tumor tissue is insufficient, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants note that the PTO has recognized that the teachings in the specification of differential expression of the PRO1557 mRNA are sufficient to establish a utility for SEQ ID NO:81, which encodes the PRO1557 polypeptide: "it is agreed that the polynucleotide of SEQ ID NO:81 has this specific utility." *Final Office Action* at page 10. The PTO similarly acknowledged the utility of the PRO1557 polypeptide-encoding nucleotide in the closely related application Serial No. 10/063,713: "The asserted utility for the nucleic acid as a tumor marker for esophageal and kidney tumor is accepted." *See Office Action for Application 10/063,713 dated June 27, 2005* at 3. In that case, the exact same data from Example 18 was relied on for utility of the claimed nucleic acids as diagnostic tools for esophageal tumors and kidney tumors, and the PTO made the same arguments regarding the insufficiency of the data in Example 18 and the cautionary teachings of Hu *et al.* Therefore, Applicants submit that the PTO's rejection of the exact same data in the instant case based on the same arguments of alleged insufficient details or the teaching Hu *et al.* are moot. As such, the data in Example 18 are sufficient to establish utility for the PRO1557 nucleic acids as a diagnostic tool.

In addition to the persuasive reasons articulated above and in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene

expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Kuo *et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1557 mRNA in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tissue, respectively. The PTO has accepted that the data in Example 18 are sufficient to establish utility for the mRNA encoding the PRO1557 polypeptide as a diagnostic tool, and therefore any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Thus, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1557 mRNA are reasonably correlated with differential expression of the PRO1557 polypeptide such that the claimed antibodies that specifically bind to the PRO1557 polypeptide have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene leads to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1557 polypeptide in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tumor tissue, respectively, it is likely that the PRO1557 polypeptide is also

differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO has cited Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) and Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302) as support for its argument that "there is sound data supporting evidence showing the unpredictability of saying level of expression of a particular nucleic acid will correlate with expression of the encoded protein." *Final Office Action* at page 9.

Applicants have previously discussed at length why the Haynes *et al.*, Gygi *et al.* and Fessler *et al.* references are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Briefly stated, references such as Haynes and Gygi, which discuss the correlation between static levels of mRNA and static levels of protein across different genes, are also not relevant – Applicants rely only on the assertion that changes in mRNA level generally lead to corresponding changes in the encoded protein level. Applicants incorporate by reference the previous arguments made regarding these issues, and will not repeat them here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants provide the following. Haynes and Gygi attempted to discover a global ratio common between all steady state mRNA levels and all steady state protein levels. The data of Haynes and Gygi indicated that the steady state ratio of mRNA level:protein level varied for different genes, and hence no global ratio existed. Based on this, the references concluded that protein levels cannot be accurately calculated from mRNA levels.

In contrast, Applicants' assertions require no knowledge of a ratio between mRNA levels and protein levels, nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants simply assert that a change in mRNA level for a particular gene typically leads to a corresponding change in the encoded protein level. *See, e.g., First Grimaldi Declaration* at paragraph 7. Haynes and Gygi were concerned with a different question, and, therefore, none of the data or conclusions of these references has any bearing on Applicants' assertions.

To exemplify the difference between these references and Applicants' asserted utilities, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a global correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the amount of protein X in condition A would be smaller than the amount of protein X in condition B, for example, having a ratio of 1:2, such that there is a correlation between the change in the level of mRNA and the change in the level of protein for a particular gene.

The PTO argues that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong.

For example, Haynes reports that the amount of protein produced by similar levels of mRNA varied by as much as fifty-fold, and that similar amounts of protein were sustained by amounts of mRNA that varied by as much as forty-fold. *Haynes* at 1863, first full paragraph. Based on these results, Haynes concludes that "protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." *Id.* Even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein.

Likewise Fessler does not provide any data that suggests that a change in mRNA levels does not lead to a corresponding change in the encoded polypeptide. In fact, the data provided by Fessler actually support Applicants' assertions. Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of these 18 proteins, a change in mRNA levels is reported for only 6 such proteins. In 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

In conclusion, Applicants have shown that the references by Haynes and Gygi are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein. In addition, Applicants have shown that Fessler's results are consistent with Applicants' assertions. Taken together, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants present herewith as Exhibit 2 a copy of a second Declaration by Dr. Polakis that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene

transcripts out of 31 gene transcripts (i.e., greater than 90%) in which a change in mRNA levels in tumor tissue compared to normal tissue along with a corresponding change in protein levels in tumor tissue compared to normal tissue, were detected. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided sufficient facts to permit the Examiner to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *Utility Examination Guidelines Part IIB*, 66 Fed. Reg. 1098 (2001).

In addition to the supporting declarations and references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 3), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved

abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 4) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 5) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 6) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 7) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 8) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2,

and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 9). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 10) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 11), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet

obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 12) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an additional 70 references (abstracts attached as Exhibit 13) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.* and Gygi *et al.*, which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 14) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et*

al. Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 15) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 16) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 17) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 18) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 19) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 20) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 21) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references and an additional expert Declaration in addition to the declarations and references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 22). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1557 mRNA is differentially expressed in esophageal tumors and kidney tumors as compared to normal esophageal tissue and normal kidney tumors, respectively, the PRO1557 polypeptide will likewise be differentially expressed in esophageal tumors. This differential expression of the

PRO1557 polypeptide makes the claimed antibodies that specifically bind to the PRO1557 polypeptide useful as diagnostic tools for cancer, particularly esophageal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies that specifically bind to the PRO1557 polypeptide. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1557 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1557 polypeptide is expressed at least two-fold higher in esophageal tumor and kidney tumor compared to normal esophageal tissue and normal kidney tissue, respectively. These data are strong evidence that the PRO1557 gene and polypeptide are associated with esophageal tumor and kidney tumor. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1557 gene and polypeptide with a specific disease. The asserted utility for the claimed antibodies as diagnostic tools for cancer, particularly esophageal tumor and kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa*, 93 F.3d at 1565 ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross*, 753 F.2d at 1050 (same); *Nelson*, 626 F.2d at 857 (same). In addition, utility need only be shown to be "more likely than

not true." *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 1-5 under 35 U.S.C. §112, first paragraph, arguing that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. *See Final Office Action* at 2. For the reasons provided above, Applicants submit that Applicants have established at least one specific, substantial, and credible utility, and the PTO's rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, as lacking utility should be reversed.

In addition, the PTO states that the claims lack enablement because one skilled in the art would not know how to use the claimed antibodies without undue experimentation. *See Final Office Action* at 4. The PTO provides an analysis of various "Wands factors" which the PTO asserts supports a finding of a lack of enablement. *See Final Office Action* at 3-4. This Wands factors analysis was based on the same arguments used in asserting that the claims lack utility: the protein did not have an art-recognized use, there is evidence that nucleic acid expression does not correlate with protein expression, and the specification does not provide sufficient experimental details. The arguments directed toward lack of enablement are interspersed with and based on the same reasoning as the arguments directed toward lack of utility. *See, e.g., Final Office Action* at 2-3, 5 and 7. Thus, the PTO demonstrates that the enablement rejection is based on lack of utility grounds. If the enablement rejection were to be based on grounds other than lack of utility, the rejections should have been imposed separately according to the M.P.E.P., which admonishes:

> To avoid confusion during examination, any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than "lack of utility" should be imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph. *M.P.E.P.* § 2107.01 IV.

The PTO did not separate the enablement rejection from the utility rejection. More importantly, the PTO's "Wands factors" analysis is not based on any argument or evidence not similarly asserted by the Examiner in holding that the claims lack utility. Applicants acknowledge that claims can be rejected as drawn to subject matter having utility while nevertheless lacking enablement; however, in the instant case, the PTO provides no reasoning and submits no evidence to support a holding that the claims lack enablement for reasons that differ from the reasoning and evidence provided for holding that the claims lack utility. Thus, by repeating the same arguments and relying on the same evidence for both the utility and enablement rejections, the PTO demonstrates that the enablement rejection is grounded solely on a "lack of utility" basis. Accordingly, the Examiner's enablement rejection is only proper if the utility rejection is proper. *See M.P.E.P.* § 2107.01 IV. Applicants have argued above that one skilled in the art would have believed the claimed antibodies have a substantial, specific and credible utility, and, thus, a utility rejection for the claimed antibodies is not proper. Applicants further submit that because a utility rejection for the claimed antibodies is not proper, the Examiner's enablement rejection of the claimed antibodies also is not proper.

Even if the PTO's enablement rejection extended beyond the utility rejection, which it does not, Applicants submit that the specification enables one skilled in the art to make and use the full scope of the claims without undue experimentation. The claimed subject matter relates to antibodies that specifically bind the polypeptide of SEQ ID NO: 82. The specification discloses how to make the claimed antibodies, for example in paragraphs [0365]-[0374] and Example 10. Similar methods also were known in the art. In addition, the specification discloses that the claimed antibodies can be used in diagnostic assays to detect the expression of PRO1557 in specific types of tissue. *See e.g., Specification* at ¶[0407]. In light of the differential expression of the nucleic acid encoding the PRO1557 polypeptide in esophageal or kidney tumors compared to normal esophageal or kidney, respectively, one of skill in the art would have expected the PRO1557 polypeptide to be differentially expressed in these tumors as well. Therefore, given the teaching in the specification on how to make and use the claimed antibodies to detect expression of PRO1557 polypeptide in specific tissues, one of skill in the art would have been enabled to practice the claimed invention without undue experimentation.

Because Applicants' specification teaches how to make and use the claimed subject matter, it must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See M.P.E.P.* § 2164.04. It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

In conclusion, in the PTO's entire analysis of the Wands factors, the PTO relies only on evidence and arguments directed to the utility rejection of the claims. Applicants have submitted overwhelming evidence demonstrating that the PTO's evidence is inconsistent with the knowledge in the art as a whole. Moreover, the PTO has not submitted any evidence demonstrating that one skilled in the art could not use the teachings of the specification to make and use the claimed antibodies in diagnostic assays to detect the expression of PRO1557 in specific types of tissue.

The PTO merely provides unsubstantiated arguments that the specification is insufficient because various experimental specifics were not provided in the specification, and without disclosing such specifics, it would require undue experimentation to use the claimed antibodies. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.P.E.P.* § 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404, citing *In re Jackson*, 217 U.S.P.Q. 804, 807-

808 (Bd. App. 1982). Based on the teachings of the specification and the level of skill in the art, it was routine to make and use antibodies such as the claimed antibodies, in, for example, detecting proteins in designated tissue samples. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the binding properties of the claimed antibodies, the ability of an antibody to bind to a sample, or specific details of sample binding. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed antibodies. The claimed invention is, therefore, fully enabled. Moreover, the PTO provides no evidence to support an assertion that, absent various specific experimental details, it would require undue experimentation to use the claimed antibodies. Absent such evidence, there is no reasonable basis to question the sufficiency of the disclosure.

In view of the above, Applicants submit that the specification, in view of the knowledge in the art, fully enables the use of the claimed antibodies. The PTO has provided no significant evidence or argument to the contrary. In view of the above, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

The PTO also maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 102(b) over WO 00/70049 (published November 23, 2000).

The Examiner asserts that "[b]ecause the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, ... and the earlier application [*sic*] likewise do not meet those requirements, the instant application does not receive benefit of priority to earlier filed applications." *Final Office Action*, at page 11.

The instant application is a continuation of, and claims priority under 35 USC § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 USC § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 USC § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 USC § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, claims priority under 35 USC § 119 to US Provisional Application 60/105881 filed 10/27/1998. The sequences of SEQ ID NOs: 81 and 82

were first disclosed in U.S. Provisional Application 60/105881 filed 10/27/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Applicants submit that, in view of the arguments above, the claimed antibodies have utility and are fully supported by the specification in accordance with 35 U.S.C. § 112, first paragraph. Moreover, Applicants submit that the previously filed applications, to which Applicants have properly claimed priority, also support the claimed antibodies. Even if it were to be determined that Applicants are not entitled to their earliest priority date, the subject matter of the present application was disclosed in, and therefore is entitled to the priority date of, PCT Application PCT/US00/23328 filed August 24, 2000. Accordingly Applicants are entitled to a priority date no later than August 24, 2000.

WO 00/70049 was published November 23, 2000. Thus, WO 00/70049 was not published more than one year prior to Applicants' priority date, as required under 35 U.S.C. § 102(b). Accordingly, WO 00/70049 cannot be prior art under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that the Examiner remove this ground for rejection of Claims 1-5.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 28, 2006

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